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MINI REVIEW

Regulation of exosomes as biologic medicines: Regulatory challenges faced in exosome development and manufacturing processes

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Abstract

With advances in medical technology, extracellular vesicles, also known as exosomes, are gaining widespread attention because of their potential therapeutic applications. However, their regulatory landscape is complex and varies across countries because of their unique intracellular mechanisms of action. The diversity of manufacturing techniques renders their standardization challenging, leading to a fragmented regulatory landscape. The current global regulatory framework of exosomes can be broadly classified into two strategies: one involves elucidating constituent components within exosomes and the other involves examining the physiological repercussions of their secretion. When using exosomes as therapeutic agents, they should be governed similarly to biological medicinal products. Similar to biologics, exosomes have been analyzed to determine their particle size and protein composition. An exosome-based therapeutic agent should be clinically approved after understanding its molecular composition and structure and demonstrating its pharmacokinetics and therapeutic efficacy. However, demonstrating the pharmacokinetics and therapeutic efficacy of exosomes is challenging for regulatory agencies. This article reviews the technical characteristics of exosomes, analyzes the trends in regulatory laws in various countries, and discusses the chemistry, manufacturing, and control requirements of clinical applications.

INTRODUCTION

Exosome therapy is in its infancy, and the industry must address safety, efficacy, and regulatory issues to realize the potential of promising exosome-based therapies. Currently, private clinics more frequently provide exosome-based therapy; however, the US Food and Drug Administration (FDA) has alerted consumers that no exosome products are currently approved.[1] These confusions are caused by the lack of regulatory standards.

Exosomes can be generated by different functional cell types; thus, they are not a single homogeneous component.[2] Exosome secretion is sensitive to culture conditions; even if they originate from the same type of cells, they may have different characteristics,[3] resulting in different stability and batch-to-batch differences. Because of their inherent instability, liquid-based exosomes are highly susceptible to degradation and alteration within a few hours after production, whether naturally or through engineering processes. This characteristic has posed challenges

in quality control testing and has led to the development of technologies, such as lyophilization and cryopreservation, for integrity and stability. After cryopreservation and thawing, further investigation is required to determine whether the exosomes are equivalent to the original.[4] These unresolved challenges have raised concerns about how to manage the quality, safety, and stability of exosomes. Furthermore, these issues have contributed to challenges in developing exosome-based products.

Considering the complexity of exosomes, analyzing global regulatory frameworks, production techniques, and existing guidelines for biopharmaceuticals could aid in establishing clearer rules governing exosomes. This review aims to provide knowledge regarding global trends and regulatory frameworks in biomedicine, thereby establishing effective governance and oversight mechanisms for exosomes.

ADVANTAGES OF EXOSOMES

Exosomes are extracellular vesicles (EVs) with a diameter of approximately 30–150 nm that are naturally produced by cells. They are responsible for the transfer of biological substances, such as proteins, RNAs, and metabolites, between cells and are crucial in cell-cell communication. They have several commercial applications and have garnered significant attention over the past decade.[5]

Exosomes have functions similar to those of cell-based products, including stem cell adjustment, tissue repair, and immune regulation. Exosomes as drug delivery systems have the benefits of natural targeting ability, no immunogenicity, nanoscale size, overcoming biological barriers (such as blood-brain–barrier penetration), oral drug formulation capability, enhanced storage capability, and natural nanoparticles with reduced safety risks; thus, these characteristics make exosomes a superior choice as EVs for drug delivery and other healthcare applications (Table 1).[6]

Recent studies have shown that mesenchymal stem cell (MSC)–derived exosomes, which are extracted from human tissues, such as the endometrium, bone marrow, and adipose tissues, have varying therapeutic effects. This highlights the effect of tissue sources on exosome efficacy. Additionally, animal models of diseases, such as epilepsy, Parkinson's disease, and stroke, demonstrated the advantages of MSC–exosome therapy. MSC-exosomes show promise in ongoing clinical studies for chronic kidney disease, graft-versus-host disease, skin hyperpigmentation, COVID-19, and osteoarthritis, exhibiting safety and efficacy in a few cases. Nevertheless, clinical applications face challenges, such as product heterogeneity, rapid systemic clearance, and long-term stability. To overcome these challenges, the standardization of doses, administration routes, and parent MSC sources is necessary. The urgent need for preclinical and clinical studies continues to push MSC–exosome therapy into practice.[7]

TABLE 1 Exosomes, as delivery vehicles, possess numerous advantages: Advantages of exosomes as delivery vehicles.

a. Natural targeting ability
b. Nonimmunogenicity
c. Nanoscale size and overcoming biological barriers
d. Blood-brain–barrier penetration
e. Oral drug formulation capability
f. Enhanced storage capability
g. Natural nanoparticle with reduced safety risks

Note: Modified from Exosomes as Carriers for Drug Delivery in Cancer Therapy Published on March 29, 2022. Surface modification of exosome membranes can be achieved through direct and indirect methods. Indirect modification refers to the engineering of exosome-releasing cells. Cell engineering methods include genetic engineering, metabolic engineering, and direct membrane engineering of parent cells.

Unlike that of cells, which may be uncontrollable with varying treatment efficacy, the biological response of exosomes is safe and more predictable. Although the duration of effect may be shorter, exosomes do not have proliferation or differentiation capabilities similar to those of cells, but they can store and carry biological substances for targeted and efficient delivery.[8]

Another advantage of exosomes is that they can be filtered or sterilized before aseptic filling. They also exhibit a relatively high tolerance to various storage conditions and can be stored by freezing or freeze-drying methods. This reduces the overall manufacturing, storage, and transport costs. Furthermore, their variability is lower than that of cells when prepared in batches. Based on these advantages, a standardized regulatory framework should be established to promote the development and use of exosome technology worldwide.[5]

Engineered exosomes can be produced on a large scale and purified to enhance the quality and purity of exosome-based drugs. As a result of the development of engineered exosomes, the quality and purity of exosome-based drugs can now be evaluated using current good manufacturing practices (GMP) quality control measures, such as particle size and quantity assays. However, these quality control measures cannot ensure the efficacy and potency of exosomes in current technology.[9] To ensure safe therapeutic applications, manufacturers must report detailed data on exosome production and characterization, implement rigorous quality controls, conduct preclinical testing, and develop in vitro-in vivo–correlated assays under regulatory oversight.[3] Currently, regulatory policies and legislation worldwide are evolving to align with these requirements.

REGULATING THE UNKNOWN

Exosomes, which carry various functional biomolecules, have unknown effects on hosts.[10] To better understand their mechanisms, specific components and underlying processes must be analyzed and investigated, similar to new drugs and biologics. Exosomes contribute to cell development and physiological changes; thus, their biosafety profiles and quality control must be individually verified. The primary standards for drug quality control are the Pharmaceutical Inspection Convention and Current Good Manufacturing Practices (cGMP) and Cooperation Scheme Good Manufacturing Practices (PIC/S GMP), which serve as the primary reference for ensuring quality during manufacturing processes.

Differences in GMP-based quality systems adopted by various countries have led to regulatory disparities.[10] cGMP and PIC/S GMP have distinct approaches for assessing the quality of cell-based products. Although both guidelines emphasize quality management systems, PIC/S GMP provides more details about organizational structures, responsibilities, and training programs than cGMP.[10] PIC/S GMP also emphasizes robust validation protocols for critical equipment, software, and processes, whereas cGMP focuses on final product quality control.[11]

This difference in regulatory focus leads to variations in exosome production and manufacturing control. In the USA, the quality system for pharmaceutical products is primarily based on cGMP, which governs certification, processing, and environmental controls throughout the production process.[10] cGMP reduces contamination, defects, and errors, providing significant benefits for mass production and regulatory approval of exosomes.

Although naturally derived exosomes can be produced, large-scale production of engineered exosomes for medical purposes is extremely promising; however, large-scale GMP–grade manufacturing is extremely complex. Even if the same cell source is used, exosome contents produced at the end may differ because of variations in growth conditions, such as temperature, media composition, and the supplements provided. This is a challenge in large-scale exosome production.[10] The advantage of engineering technologies for exosome production is that they can ensure a self-controlled production environment, allowing for the production of exosomes with higher concentrations and more uniform quality. This encompasses the manufacturing process and subsequent fill and finish steps and the monitoring of storage conditions and control of distribution pathways, all in a manner compliant with regulatory and GMP requirements.

Minor changes during exosome cultivation may alter their biological characteristics. Even if they originate from the same parent cell, variations in the cultivation conditions, such as cell passage number, culture method, and culture medium, can result in different exosomes. Thus, a regulatory approach for cell therapy may not be suitable for exosome therapy because the efficacies of exosomes produced by the same cells under different conditions may differ. Therefore, similar to the verification of the mechanism of action for biologics, rigorous regulation of exosomes is extremely important.

Natural exosomes encapsulate various regulatory proteins, microRNAs (miRNAs), messenger RNAs (mRNAs), and other naturally active substances, demonstrating excellent therapeutic effects and serving as an important form of exosome-based therapies.[12] Exosome product concentration is typically assessed by particle count, size distribution, and particles per microgram of protein (particles/μg). However, different methods can yield significantly varying results for particle size and concentration measurements, highlighting the need for standardized approaches.[13]

UNLOCK THE SECRET OF EXOSOME'S MECHANISM OF ACTION

The identification, quantification, and characterization of the main substance(s) responsible for a drug's pharmacological, immunological, or metabolic action is crucial in the development of exosome-based drugs. The mechanism of action (MOA) of an exosome-based drug product is determined by both the active drug substance encapsulated in exosomes and the characteristics of exosomes (such as size), which may affect the distribution and metabolism of the drug product. Therefore, quality control of exosomes is critical. The analysis of active substances is vital for defining appropriate strategies to control the quality of exosomes.[14]

In the early phases of biological drug manufacturing development, a pragmatic and feasible approach is commonly adopted. The standard operating procedures can ensure high batch consistency, even with repeated manufacturing processes. To assess batch-to-batch consistency, freshly prepared batches are evaluated against previously manufactured products using biochemical, biophysical, and functional assays.[12] Drugs can be verified through analytical techniques such as high–performance liquid chromatography (HPLC) or gas chromatography-mass spectrometry (GC-MS) to ensure composition and quality. However, these methods are not directly applicable to exosome-based products because of their unique properties.[2] Because of the limitations of HPLC and GC-MS, these methods are not suitable for detecting exosome

material. Consequently, it is crucial to verify the quality of exosomes before proceeding. In this context, electron microscopy, dynamic light scattering, and flow cytometry are valuable tools for determining the size and number of exosomes. Currently, quality control and production development in the exosome field focus on monitoring the particle size and number distribution rather than content validation.[10]

To address the gap in quality management systems for exosome products, regulatory measures and directions have been proposed, similar to those used in the biological pharmaceutical industry. The International Society for Extracellular Vesicles has established Minimal Information for Studies of Exosome guidelines to promote their clinical use. Practical checklists, including quantification and characterization of exosomes, are included in the guidelines for researchers and clinicians.[15]

Both biologics and exosomes prompt the desired primary effects through their MOA.[16] Thus, the MOA of exosomes should be understood for developing effective treatments. Elucidating therapeutic substances responsible for a particular therapeutic outcome facilitates researchers in developing more comprehensive and stringent quality control systems for exosome products.

REGULATORY FRAMEWORK

The current global regulatory framework for exosomes can be broadly categorized into two primary approaches: one on elucidating the impact of exosome content on physiological functions and the other on examining the methods used to obtain exosomes (Table 2). In addition to noncellular characteristics and purification selectivity, product verification remains a challenge. Regulatory agencies in various countries strive to establish a framework that balances safety and efficacy.

UNITED STATES

The US FDA regulates the therapeutic effects of products; thus, most therapies and products based on EVs and stem cells are currently being overseen by the US FDA's Center for Biologics Evaluation and Research (CBER). According to US regulations, exosome products are governed by the Public Health Service (PHS) Act Section 351, which regulates human cells, tissues, and cell- and tissue-based products (HCT/P). These products are managed by the Office of Therapeutic Products, under the US FDA's CBER. In some cases, products may require evaluation by multiple centers. In 2019, the US FDA issued safety notices and consumer alerts to address advances in technology and the gap in regulatory control for regenerative medical products (exosome products).[17]

Following reports of adverse events experienced by patients treated with exosome products, the US FDA issued a public safety notification. As of October 2023, the US FDA had issued six warning letters regarding exosome products. These products are regulated as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act (FD&C) Act and/or the PHS Act and are subject to additional regulations, including appropriate premarket review. Exosome products marketed for the treatment of human diseases and conditions are regulated as drugs under the FD&C Act and biological products under the PHS Act and are subject to premarket review and approval requirements.[18]

EUROPE

The European Directive (Directive 2001/83/EC and Regulation 1394/2007/EC) states that exosomes directly purified from cells or from translated RNA are not considered advanced therapeutic medicinal products (ATMPs) and are classified with biological specifications. However, if exosomes contain functionally translated RNA and patients have expected therapeutic outcomes following administration, they are classified as ATMPs, a broad term used to group three medicinal product classes intended for human use, encompassing somatic cell therapy, gene therapy, and tissue-engineered medicines. Tissue- or cell-based therapies are regulated as ATMPs and are evaluated by the Committee for Advanced Therapies (CAT) at the European Medicines Agency (EMA). The CAT is a specialized committee responsible for all ATMP–related activities.[19]

For example, an exosome product containing a regulator protein and microRNA-17 based on the EMA/CAT falls within the definition of a gene therapy medicinal product because it is a biological medicinal product containing active substances consisting of recombinant nucleic acids. Its therapeutic effect directly relates to the recombinant nucleic acid. Thus, the EMA/CAT considers the product to fall within the definition of a gene therapy medicinal product as provided in Article 2[1] of Regulation (EC) No 1394/2007.[20]

JAPAN

In Japan, products related to regenerative medicine are considered regenerative medicine products and are governed by the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices

TABLE 2 Different regulatory standards for exosomes.

Country	USA	Europe	Japan	South Korea	Taiwan
Classification criteria	Contents of exosomes can affect physiological function		Based on how exosomes are obtained		
Regulatory unit	USFDA	EMA	MHLW & PMDA	MFDS	TFDA
Product classification	Mechanism of action (MOA) provides sufficient preclinical and clinical research data to demonstrate the safety and efficacy: Biomarkers for disease diagnosis or Therapeutic products[a]	Includes functional translated RNA (ATMP) Excludes functional translated RNA (Biologics)	Nonliving cell–containing medications	Drugs manufactured by isolating and purifying extracellular vesicles secreted by living cells	Derivatives included in regenerative medicine
Quality Control Point	cGMP Product Development Chemical Manufacture Control (CMC) Regulations to assure that the quality is built into the design and manufacturing process at every step	PIC/s GMP Regulation from the source of raw material production to the end of consumer use	PIC/s GMP Regulation from the source of raw material production to the end of consumer use	PIC/s GMP Regulation from the source of raw material production to the end of consumer use Guideline on Quality, Nonclinical, and Clinical Assessment of Extracellular Vesicle Therapeutic Products	PIC/s GMP Regulation from the source of raw material production to the end of consumer use Guiding principles for manufacturing control and development strategies for extracellular vesicle preparations (Draft)

Note: Regulatory standards for exosomes vary worldwide, depending on their characteristics. They are based on whether the exosome content can affect physiological functions in the USA and Europe and based on how they are obtained in Japan, South Korea, and Taiwan. These guidelines are intended to ensure that pharmaceutical products are consistently produced and controlled with high standards of quality, safety, and efficiency. This includes provisions for ensuring the proper documentation and traceability of pharmaceutical products throughout their lifecycle, from raw material procurement to distribution and use.

[a]Reference compilation: Cheng, K. & Kalluri, R. Guidelines for clinical translation and commercialization of extracellular vesicles and exosomes based therapeutics. *J. Extracell. Vesicles.* **2**, 100029 (2023).

Agency (PMDA). To gain marketing approval, human clinical trials and a Marketing Authorization Application should be conducted by all applicants, followed by obtaining marketing authorization upon review. The PMDA indicated that cell and gene therapy products are classified as distinct product categories known as regenerative medicine products. In contrast, nonliving cell–containing exogenous preparations are not considered regenerative medicinal products or devices. Instead, they may be classified as medications because their modes of action are primarily based on pharmacological, immunological, or metabolic mechanisms. Exosomes are categorized as biologics in Japan and are subject to the same regulatory requirements as vaccines, blood products, and other biologics.[21] Noncommercial clinical studies on external preparations for medical use are managed on a case-by-case basis by physicians outside the scope of regenerative medicine because these preparations lack living cell components and are not considered specific processed cells.[22]

SOUTH KOREA

The Ministry of Food and Drug Safety (MFDS) is the administrative unit that regulates and supervises regenerative medicine–related preparations in South Korea. The agency classifies regenerative medicine–related preparations as biologics and manages their marketing. The guidelines established by the Korean Society for Extracellular Vesicles (KSEV) for exosomes are similar to those set by the International Society for Extracellular Vesicles (ISEV). These guidelines provide quality, nonclinical, and clinical considerations for developing EV-based products and ensure their safety and efficacy. Consequently, they have contributed to the rapid development of exosomes in esthetic medicine in Korea. However, no medicinal exosome products have been approved for marketing to date.

The National Institute of Food and Drug Safety Evaluation (NIFDS) of Korea released the Guideline on Quality, Nonclinical, and Clinical Evaluation of Extracellular Vesicle Preparations in December 2018.[23] This guideline applies to exosomes produced from human cells. Based on the definition of EV preparations, these include drugs manufactured by isolating and purifying exosomes secreted by living cells. If EV mimics are used to develop drugs, this guidance may apply; however, further considerations are expected.

TAIWAN

In Taiwan, the Regenerative Medicine Development Act defines regenerative medicine to encompass derivatives, such as exosomes.[24] Furthermore, Taiwanese regulatory agencies have referenced guidelines and standards from various countries and organizations, incorporating PIC/S GMP principles and adding safety and efficacy testing provisions. The Center for Drug Evaluation (CDE) published the draft guideline for the developmental strategy of manufacturing control for cell-free vesicle-based drug products in September 2023. This guideline references the ISEV, minimum information for studies of extracellular vesicles 2018 (MISEV 2018), PMDA, and MFDS, among other relevant organizations. The guideline covers the following topics: "Raw Material Control," "Exosome Preparation, Separation, and Concentration," "Characterization," "Quality Control of Exosome Preparations," and "Stability of Exosome Preparations." Inspections are conducted at the raw material stage to ensure compliance with government policies and facilitate the establishment of industry standards, paving the way for the Taiwan Contract Development and Manufacturing Organization (CDMO) industry to expand into the market.

In 2022, over 56% of new drug marketing authorization holder companies globally operated CDMO businesses concurrently. Asian CDMOs primarily provide raw materials as their main service, accounting for up to 92% of all Asian CDMO services. Emerging therapeutic areas, such as gene therapy, cell therapy, exosomes, and nucleic acid drugs, are actively being developed.[25] Leveraging Taiwan's strengths in small-scale rapid manufacturing in the tech and biotech industries, a CDMO business was actively developed. The National Institutes of Health's ClinicalTrials.gov database (https://clinicaltrials.gov/) in 2024 indicated that eight clinical trials on exosomes were being conducted in Taiwan, accounting for 3.75% (8/213) of all cell-based clinical trials. The authors predict that the proportion of exosomes in clinical applications will significantly increase after the draft is passed, particularly with the active guidance of policies promoting the establishment of the CDMO industry.

CONCLUSION

The lack of official approval for injected exosome products worldwide may be attributed to the variability and impurity of exosome preparations. Furthermore, the specific MOA remains poorly understood, hindering the development of quality control procedures. Best practices for quality control depend on an understanding of the MOA, which is crucial for the function and efficacy measurements required for quality management approval. Under GMP regulations, physical controls on exosome quality are still basic. Advanced analytical techniques can be used

to effectively evaluate exosome composition and purity in future, potentially leading to clearer regulatory oversight akin to biological products.

Considering current regulatory measures and policy strategy, clinical trials should be conducted on exosomes to confirm their MOA. A more comprehensive quality monitoring should also be performed to identify the complex exosome content and the limitations of current testing methods. Various countries are establishing monitoring and reporting databases to provide relevant big data and to inform future policy and regulatory directions. To ensure quality and safety, regulatory oversight units may establish standards for professional knowledge regarding cellular activity and drug effects, including mechanisms of action. Industry standards for manufacturing and controlling active cellular products may also be established, including automated processes and purification techniques.

AUTHOR CONTRIBUTIONS

C.K.W. wrote the manuscript. C.K.W. and C.H.L designed the research. C.K.W. performed the research. C.K.W. and T.H.T. analyzed the data.

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The authors declared no competing interests for this work.

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